REMARKS

Status of the Claims

Claim 1 is amended herein to recite that the liquid pharmaceutical composition comprises levocetirizine or a pharmaceutically acceptable salt thereof and a preservative mixture consisting essentially of a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight, said mixture being present in an amount of more than 0 and less than 1.125 mg/ml of the composition, and that the composition is substantially free of bacteria. This amendment is intended to indicate that no operative quantities of any other preservative components or antibiotic ingredients are present in the composition. Previously withdrawn claims 7-9, which recited the presence of other preservative components, are hereby cancelled. Previously withdrawn claim 10, which recited that the active ingredient is cetirizene, is hereby cancelled.

Claim 14 is amended to correct the dependency.

New claim 28 is directed to the embodiment set forth at page 12, Table 16 of the application as originally filed.

New claim 29 is directed to the embodiment set forth at page 13, Table 18 of the application as originally filed.

If the present amendments are found to place claims 1, 2, 5, 12, 14, 15, 17 and 27 in condition for allowance, then the Examiner is authorized to cancel without prejudice previously withdrawn method claims 18-26 by Examiner's amendment. Applicants expressly reserving the right to pursue the subject matter of those claims in one or more continuing or divisional applications.

Submitted herewith in support of this application is the Declaration of Domenico Fanara Under 37 CFR 1.132. Mr. Fanara is the first-named inventor of the present application.

New Claims

New claims 28 and 29 recite specific levels of levocetirizine, methyl paraben, and propyl paraben. Submitted herewith is experimental evidence demonstrating the unexpected results

achieved by these compositions, namely, that the compositions remain substantially free of bacteria while maintaining levels of parabens substantially below the levels taught by the prior art as being necessary (Decl. ¶¶ 8,9). It is respectfully submitted that these claims are not obvious over the art of record.

Supplemental IDS

Submitted with the Supplemental IDS is a more complete copy of one of the references previously submitted on September 3, 2010.

Rejection of claims 1-2, 5, 12, 17 and 27 under 35 USC 103

Claims 1-2, 5, 12, and 17 stand rejected as obvious over DeLongueville et al. (WO 02/47689 A2), Gilliland 1 (1992, *J. Appl. Bacteriol.*, 72: 252-57); and Gilliland 2 (1992, *J. Appl. Bacteriol.*, 72:258-61) and Doron et al. P2001 *Int'l J. Antimicrobial Agents* 18: 575-578) in view of Routledge (1998; *Toxicol. Appl. Pharmacol.*; 153:12-19). In light of the foregoing amendments and arguments presented below, this rejection is respectfully traversed.

The presently claimed invention is based, at least in part, on the surprising finding that the active substances belonging to the family of substituted piperazines, such as levocetirizine, possess a preservative effect in aqueous solutions (specification, page 2, lines 4-6), thereby enabling use of lesser amounts of preservatives such as parabens. Independent claim 1 as amended is directed to a composition comprising levocetirizine and a preservative mixture consisting essentially of methyl parahydroxybenzoate (methyl paraben, hereinafter "MP") and propyl parahydroxybenzoate (propyl paraben, hereinafter "PP") in a ratio of 9/1 by weight, said mixture being present in an amount of more than 0 and less than 1.125 mg/ml of the composition. Surprisingly, levocetirizine has antimicrobial properties (*Id.* and Decl. ¶ 7), such that the presence of levocetirizine in the composition in combination with the 9:1 MP/PP ratio, allows for the use of low levels of total parabens and essentially no other preservatives, while maintaining the liquid composition substantially free of bacteria. This is particularly important for a liquid pharmaceutical composition, which is susceptible to microbial contamination when the seal on the packaging is opened and the contents are subject to repeated contact with dosing implements. (Specification, page 1, line 27 – page 2, line 3; Decl. ¶ 4)

This result is even more surprising when one considers that other liquid pharmaceutical compositions use significantly greater amounts of preservatives, typically about 2 mg/ml of total parabens, as shown by the references submitted with the response of May 4, 2010, Decl ¶ 5). This argument does not "ignore the teachings of the record" (July 27, 2010 Office Action, page 4, line 1). These additional references provide evidence as to what those skilled in the pharmaceutical arts understand to be necessary levels of preservatives in liquid pharmaceutical compositions. Further, these references are more relevant than the references cited by the Office, because these references each disclose pharmaceutical compositions, while the Gilliland 1, Gilliland 2, and Doron references cited by the Office do not disclose pharmaceutical compositions.

It is respectfully submitted that the present rejection is based on the selection of different parameters out of different references, suggesting without support that it would have been obvious that the combination of these different parameters would have resulted in a liquid pharmaceutical composition substantially free of bacteria. DeLonguevlle, commonly owned by the assignee herein, teaches compositions of cetrizine with methyl-and propyl paraben but does not teach such compositions with levocetirizine and teaches nothing about the ratios and amounts of methyl and propyl paraben. (Decl. ¶11) None of the other references relates to levocetirizine compositions, and none suggests that it is possible to achieve a liquid levocetirizne pharmaceutical composition that is substantially free of bacteria with the preservative concentration recited in the present claims.

Doron describes a study "as a step in optimizing the concentration of parabens as antibacterial agents in the oral cavity" (Doron at 575-576). Doron teaches one composition wherein MP/PP is 4/1 and overall parabens is 1.55 mg/ml, and another composition wherein MP/PP is 8.33/1 and overall parabens is 2.8 mg/ml. These compositions respectively have parabens levels 37% and 248% greater than the maximum parabens level of the present claims. This reference does not suggest that the total parabens in a liquid pharmaceutical composition could be reduced to 1.125 mg/ml or less, and suggests nothing about the effect of the presence of levocetirizine. In fact, this reference teaches away from the present invention by teaching that a higher MP/PP ratio requires greater level of total parabens. (Decl ¶ 14) It is improper to rely on

Doron for its teaching of an MP/PP ratio without also recognizing its teaching regarding total paraben concentration, because the reference must be considered for *all* that it teaches.

With respect to Gilliland 2, the Office cites the following compositions:

MP/PP	Conc., mg/ml
8.6/1	1.34
10/1	1.32
10/1	1.54
11.7/1	1.52

The *minimum* preservative level of 1.320 mg/ml is 17% greater than the 1.125 mg/g *maximum* preservative level recited in the present claims. Moreover, this composition did *not* destroy E.coli, as shown in Fig. 5 at the curve for "L methyl + L propyl." The fact that these compositions bracket the claimed MP/PP ratio of 9/1 does not make the claims as a whole obvious where the claim is based on the combination of the ratio, the concentration level, the presence of levocetirizine, the absence of other preservatives, and the fact that the composition remains substantially free of bacteria.

The statement that "With respect to the *amounts*, the use of lower amounts of a 9/1 ratio is suggested by the largest antimicrobial activity taught by Doron taken together with the ratios of Guilland 2" (July 27, 2010 Action, pp.4-5) is respectfully traversed. The largest antimicrobial activity achieved by Doron is with an amount of parabens 37% greater than the maximum amount presently claimed; and the minimum amount of parabens used by Guilland 2 is still 17% greater than the maximum amount presently claimed. These references, taken alone or in combination, do not teach or suggest the amount of parabens in a pharmaceutical composition as recited in independent claim 1.

The July 27, 2010 Action states at page 5, "This [greater microbial efficiency at higher ratios of MP/PP] permits less of the combination to be used to still achieve the *same* level of antimicrobial activity in a solution. This benefit would have been expected for a combination with a drug, also." (emphasis added) Even if this unsupported statement were true, the invention herein does not lie in achieving the *same* level of antimicrobial activity, the invention lies in achieving *greater* levels of antimicrobial activity at the recited concentration and MP/PP

ratios due to the presence in the solution of a particular drug, namely, levocetirizine. Thus, taking the Examiner's assertion as true substantiates the non-obviousness of the presently claimed compositions.

The July 27, 2010 Action states at page 8 that there is no limitation in the claim regarding resistance to bacteria. Claim 1 has been amended to recite that the claimed composition is substantially free of bacteria. Thus, even if Doron and Guillard 2 suggest "some" antimicrobial activity, they do not render the claimed invention obvious because they do not suggest that the compositions disclosed therein will remain substantially free of bacteria. (Decl ¶¶12-15)

The Action states at pages 9-10 that the claims are written in an open form that allows the presence of other antimicrobial agents. Claim 1 has been amended so that the preservative mixture consists essentially of methyl paraben and propyl paraben, thereby excluding functionally significant amounts of other preservatives. Other claims reciting the presence of other preservatives have been cancelled.

It is respectfully submitted that in view of the foregoing claim amendments, the claims are now commensurate in scope with the evidence of unexpected results, as acknowledged by the Office.

As all bases of rejection have been addressed by the foregoing amendments, a Notice of Allowance is requested.

If there are any questions or comments regarding this application, the Examiner is encouraged to contact the undersigned in order to expedite prosecution.

Respectfully submitted,

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/Sandra B. Weiss/
Sandra B. Weiss
Registration No. 30,814

McDonnell Boehnen Hulbert & Berghoff LLP
300 South Wacker Drive
Chicago, IL 60606

Telephone: 312-913-0001
Facsimile: 312-913-0002